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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/929,546	08/13/2001	Neil H. Bander	266/186	3868

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EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/929,546	BANDER, NEIL H.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 58-111 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 58-111 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6,12 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Preliminary Amendment filed 07-12-2002 (Paper No. 13) is acknowledged and has been entered.

Claims 38-57 were cancelled.

Claims 58-111 were added and are currently pending.

Specification

The specification is objected to on page 46, line 27 for reciting "nucleotide" since the sentence is in reference to an amino acid sequence.

The specification is objected to on page 48, line 17 for reciting "nucleotide" since the sentence is in reference to an amino acid sequence.

The specification is objected to on page 49, line 15 for reciting "nucleotide" since the sentence is in reference to an amino acid sequence.

Claim Objections

Claims 73, 75, 77, 81, 83 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The objected claims all depend from Claim 72 or 78, Markush-type claims drawn to *discrete* antigen binding portions. However, the objected claims are broader in scope than Claims 72 or 78 because they include different antigen binding portions than those claimed in Claim 72 or 78. For example, Claim 73 includes an antigen binding portion of an amino acid sequence of the variable heavy

chain produced by hybridoma having ATCC deposit no. HB-12126 *and* an antigen binding portion of an amino acid sequence of SEQ ID NO:19 (variable light chain) *or* an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12126. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are so unclear that no meaningful interpretation can be made as to what exactly the antigen binding portions comprise. For example, Claim 73 includes an antigen binding portion of an amino acid sequence of the variable heavy chain produced by hybridoma having ATCC deposit no. HB-12126 *and* an antigen binding portion of an amino acid sequence of SEQ ID NO:19 (variable light chain) *or* an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12126. Are these portions conjugated to one another? Are they separate? What exactly is meant by including the term "and" ? What is meant by including the term "or" ? Hence, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to methods of treating or preventing *non-prostate* cancers in a subject comprising providing an antibody or antigen binding portion thereof which binds to the extracellular domain of prostate specific membrane antigen (PSMA) wherein the antibody or antigen binding portion thereof binds to vascular endothelial cells proximate to or within the non-prostate cancerous cells.

However, the specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. First, the claims are

broadly drawn to a method of "preventing" or "delaying development" of any and all non-prostate cancers including renal, urothelial, colon, rectal, lung, and breast cancers and or metastatic adenocarcinoma to the liver (Claim 60). Those of skill in the art of oncology recognize that the state of the art of cancer prevention is highly unpredictable, and it not likely that physicians would recommend the preventive administration of antibodies (including those with radiolabels and cytotoxins) to individuals who have not been clinically confirmed to have such cancers. Furthermore, reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent.

Furthermore, with regards to the treatment of subjects *with* cancer comprising the presently claimed antibodies, the specification does not provide sufficient guidance and or objective evidence that such methods would predictably and effectively function to treat a subject as claimed.

Those of skill in the art also recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of

the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). Further, the disclosure provides no objective evidence or working examples to lend one of ordinary skill in the art a reasonable expectation of success. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Claims **68-73, 76-79, and 82-111** are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure with regards to the claimed hybridomas and monoclonal antibodies. Without a publicly available deposit, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Thus, applicants' referral to the four hybridoma deposits on page 35 of the specification is an insufficient assurance that all of the conditions of 37 CFR sections 1.801 through 1.809 have been met. Although applicants state that the deposits were made under the provisions of the Budapest Treaty, applicants do not state that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if the depository cannot dispense viable samples. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Claims 66, 73, 75, 77, 79, 81, and 83 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 66 is drawn to an antibody which is an IgG which have no clear support in the specification and the claims as originally filed. Hence, this is a new matter rejection.

With regards to Claims 73, 75, 77, 79, 81, and 83, the specification does not appear to have support for antigen binding portions conjugated to one another. For example, Claim 75 is drawn to antibody or antigen binding portion thereof that comprises an antigen binding portion

of an amino acid sequence from SEQ ID NO:8 *and* an antigen binding portion of an amino acid sequence from SEQ ID NO:19. However, the specification only supports those antigen binding portions selected from the group consisting of SEQ ID NO:8, SEQ ID NO:19, an amino acid sequence of the variable heavy chain produced by the hybridoma having ATCC deposit No. HB-12126, and an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit No. HB-12126.

Although, the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP § 714.02 and § 2163.06 ("Applicant should specifically point out the support for any amendments made to the disclosure.")

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 58-63, 67-69, 84-87, and 107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No.

6,136,311. Although the conflicting claims are not identical, they are not patentably distinct from each other because the currently claimed method of a method for treating non-prostate cancer in a subject comprising providing an antibody or antigen binding portion thereof which binds to the extracellular domain of PSMA wherein the antibody or antigen binding portion thereof binds to vascular endothelial cells proximate to or within the non-prostate cancerous cells reads on the patented claims drawn to methods of killing or ablating non-prostate cancerous cells with a monoclonal antibody to PSMA. Further, both methods require that the antibodies, when contacted with an extracellular domain of PSMA, be internalized with PSMA. Thus, although not identical, the claimed methods are not patentably distinct from each other.

Claims 144-171, and 178-181 are **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38, 41, 55-56, 58, 60-63, 65-66, 69, 81-118, 124-174 of copending Application No. 09/357707 (recently allowed, but not issued) Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim obvious variations or species of the same antibodies (See reasons set forth above, too.)

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
August 21, 2003